The Impact of Antimicrobial Resistance on the Delivery of Safe and Effective Healthcare

Reason	*Explanation*
Commercial Activities	***Information contained in this report is related to commercial activities and Auckland DHB would be prejudiced or disadvantaged if that information was made public.***
Prejudice to Health or Safety	***Information about measures protecting the health and safety of members of the public is enclosed in this report and those measures would be prejudiced by publication at this time.***

May not be released in public until: To be decided by the Board

Recommendation

That the Hospital Advisory Committee receives the Impact of Antimicrobial Resistance on the Delivery of Safe and Effective Healthcare report.

[redacted]

Glossary

Acronym/term	Definition
AMR	antimicrobial resistance
DALY	disability-adjusted life-years
HAI	healthcare-associated infections
MRSA	methicillin-resistant *Staphylococcus aureus*
WHO	World Health Organisation

1. Introduction/Background

Antimicrobial resistance has been recognized as a global public health threat by the World Health Organisation (WHO), United States Centers for Diseases Control and Prevention, European Centers for Disease Prevention and Control and Ministries of Health from WHO membership countries including New Zealand.

New antimicrobial resistance (AMR) mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death.

Bacteria are required to adapt to a variety of environments; when exposed to antibiotics random mutations occur in their DNA. Favorable mutations lead to the development of resistance to that antibiotic, termed selective pressure. Resistance is easily transferred from one bacterium to another. Some bacteria are intrinsically resistant to several classes of antibiotics; acquisition of resistance genes makes them resistant to most other classes of antibiotics – termed pan-resistant.

Antimicrobial resistance develops following selective pressure but it spreads because of poor infection control, inadequate sanitation and through poor food handling practices, figure 1. Since the late 1990s international air travel has grown by ≈ 6% per year, and ≈900 million passengers were

transported across international borders during 2010. In 2014 it was estimated that ≈ 81 million migrant workers were present in different parts of the world and certain developed countries such as Australia, Canada, New Zealand, Spain and the United States of America, each received an influx of >100,000 legal foreign workers during 2005.[1]

Infections caused by antimicrobial resistant pathogens are associated with increased mortality; the burden is disproportionally higher in low and middle income countries.[2] Patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) are estimated to be 64% more likely to die than those infected with susceptible strains of *S. aureus.* Across Europe, an estimated 25,000 people die each year as a result of hospital infections caused by the following five resistant bacteria:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Enterococcus faecium*
- *Pseudomonas aeruginosa*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)

Without effective antimicrobials for prevention and treatment of infections, medical procedures such as organ transplantation, cancer chemotherapy, diabetes management and major surgery (for example, caesarean sections or hip replacements) become very high risk.

In many countries, antibiotics are dispensed without professional oversight and use in both humans and animals is excessive. Whilst this is not the case in New Zealand, rates of dispensing in the community are high.[3] The Health Quality and Safety Commission Atlas of Healthcare Variation recently released an atlas titled 'Community Use of Antibiotics'.[4] The key findings from this were that:

- Of people who visited their GP in 2017, around half were dispensed at least one systemic antibiotic.
- Antibiotic use was highest in the youngest and oldest.
- Some antibiotics are prescribed 37 percent more in winter than in summer.
- Eighty-three percent of penicillins dispensed are broad-spectrum.
- The dispensing of antibiotics specifically indicated for urinary tract infections increased sharply with age and for people living in aged residential care.
- On average, 32 and 33 percent of people were dispensed an antibiotic within 30 days of a medical and surgical admission, respectively.

[1] Van der Bij AK, Pitout JDD The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae. J Antimicrob Chemother 2012; 67: 2090-2010

[2] Peters L, Olsonl., Khu DTK, et al. Multiple antibiotic resistance as a risk factor for mortality and prolonged hospital stay: a cohort study among neonatal intensive care patients with hospital-acquired infections caused by Gram-negative bacteria in Vietnam. PLos ONE 14(5):e0215666

[3] Duffy E, Ritchie S, Metcalfe S, Van Bakel B, Thomas MG Antibacterials dispensed in the community comprise 85-95% of total human antibacterial consumption J Clin Pharm Ther 2018;53:59-64

[4] https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/community-use-of-antibiotics/ Accessed 20th May 2019

Figure 1. Causes of Antibiotic Resistance

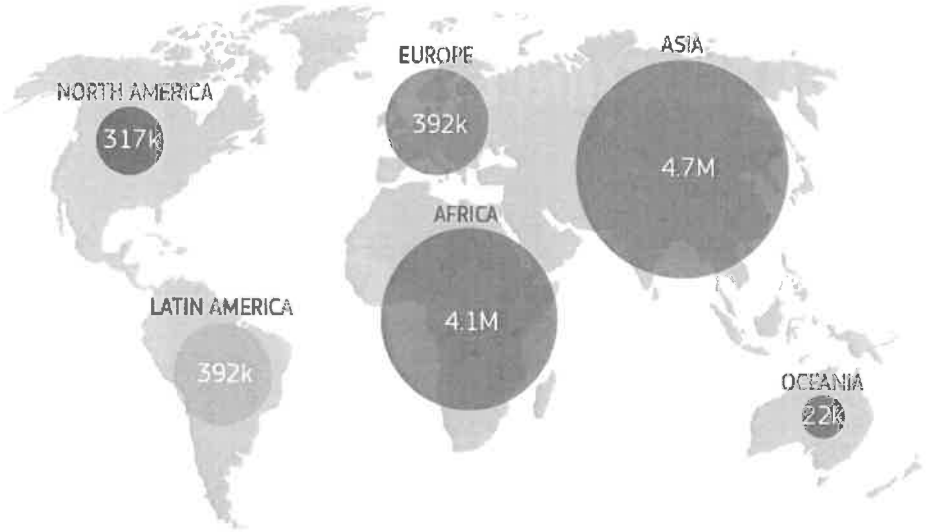
Although drug resistance affects high-income and low-income countries alike, high income countries may be better equipped to respond to the AMR crisis, and thus feel less urgency about tackling the problem proactively. The greatest burden of AMR will be felt in low and middle-income countries, figure 2.

A study from Europe estimated the incidence of infection with antibiotic resistant bacteria of public health concern measured in the number of cases (patients with infections due to antibiotic-resistant bacteria), attributable deaths and disability-adjusted life-years (DALYs). It highlighted that all age groups were affected but that the burden was greatest in the < 1-year olds and among adults it increases with age. Three quarters are associated with healthcare-associated infections (HAI) and the estimated DALYs is similar to the combined rates for influenza, tuberculosis and HV infections. Potentially 25% of all HAI were caused by antibiotic resistant bacteria; half of all HAI are considered preventable and decreasing this burden requires increased infection prevention measures. Attributable number of deaths between 2007 and 2015 had increased by a factor of 2.46.[5] Similar work from Switzerland (population 8.3 million) using the same methodology, estimated that in 2015 there were 7156 cases of infections with antibiotic resistant bacteria which accounted for 276

[5]Cassini A, Högberg LD, Plachouras D et al Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015; a population-level modelling analysis. Lancet Infect Dis 2019; 19: 56-66

attributable deaths and 7400 DALYs.[6] If the current resistance trends are not reversed it is estimated that by 2050 there will be 10 million deaths per year from infections caused by resistant bacteria.[7]

Figure 2.



Number of deaths per year attributable to AMR by 2050 if current resistance rates increased by 40%

The answer is not just to produce more antimicrobials. It has been 30 years since a new class of antibiotic was introduced that has activity against Gram negative bacilli such as *E. coli*, figure 3.[8] The two most recent new classes of antimicrobials, lipopeptides and oxazolidinones, only have activity against Gram positive bacteria such as *S. aureus* and *Enterococcus* sp.

It takes many years and lots of funding to do the research and development needed to bring a new antibiotic to market. However:

- Most new compounds fail
- Even when they succeed, the payoff is small: an antibiotic doesn't sell as well as a drug that needs to be taken daily. The financial incentive for pharmaceutical companies just isn't there.[9]
- Most of the newer antimicrobials in development are 'variations on the theme'
- Novel antibiotic are slow to come to market and may be withdrawn after post-marketing surveillance identifies significant adverse effects

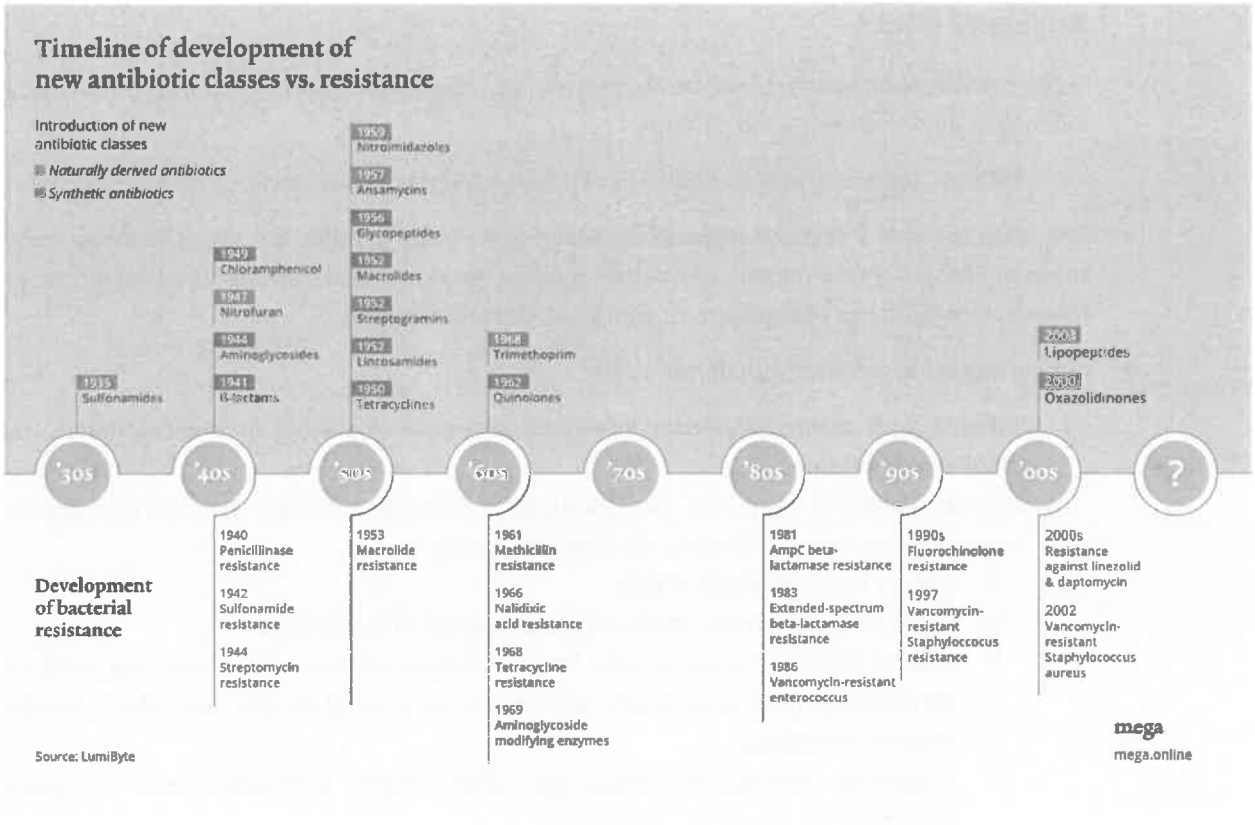
[6] Gasser M, Zingg W, Cassini A, Kronenberg A and the Swiss Centre for Antibiotic Resistance. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in Switzerland. Lancet 2019; 19: 17-8

[7] https://ec.europa.eu/health/amr/sites/amr/files/amr_factsheet_en.pdf Accessed 20th May 2019

[8] https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance Accessed 20th May 2019

[9] Singer AC, Kirchelle C, Roberts AP. Reinventing the antimicrobial pipeline in response to the global crisis of antimicrobial-resistant infections (version 1; referees:2 approved) F1000Research 2019; 8: 238. https:/doi.org/10.12688/1000research.18302.1

Figure 3. Antibiotic discovery and resistance development



As of December 2018, approximately 42 new antibiotics with the potential to treat serious bacterial infections are in clinical development. The success rate for clinical drug development is low; historical data show that, generally, only 1 in 5 infectious disease products that enter human testing (phase 1 clinical trials) will be approved for patients.[10]

AMR has impacted on the health of New Zealanders for over 50 years, figure 4. However, the burden of AMR has increased significantly since the 1990s with the impact being greatest in the Auckland region. Auckland residents travelling to and from low and middle income countries with high burden of AMR, such as countries within Asia, are at risk of exposure to antibiotic resistant bacteria in foods and the environment. As a result gut colonisation may occur; this may clear over months to years but poses a risk to the person if they require medical interventions in the interval. Equally, any individual receiving medical care in countries with high burden of AMR are likely to become colonised with an antibiotic resistant bacteria. Within the Pacific, antibiotic resistant bacteria are becoming endemic in some hospitals. Patients transferred from these hospitals to Auckland DHB are likely to be colonised with these antibiotic resistant bacteria. Patients transferred within New Zealand may also pose a risk if within-hospital transmission of antibiotic resistance bacteria is occurring.

[10] Antibiotics currently in global development. The PEW Charitable Trust, March 2019 pewtrusts.org/antibiotic- pipeline

2. How will this impact on the delivery of effective clinical services within Auckland DHB?

- Our most vulnerable patients will be at greatest risk – neonates, patients requiring intensive care and highly immunosuppressed patients
    - Patients colonised with an antibiotic resistant bacteria may be declined for transplantation
- The rates of some infectious diseases on Māori and Pacific peoples are about twice as high as those of European descent and other ethnic groups. As a consequence Māori and Pacific peoples have an increased risk of exposure to antibiotic resistant bacteria.[11]
- Increased cost associated with delivery care
    - Patients with community-onset infections previously managed in the community may require hospital care
    - Patients admitted from the community with infections caused by antibiotic resistant bacteria are at risk of increased morbidity and mortality
        - Longer hospital length of stay
        - Likely to require more interventions to manage the infection
        - Antimicrobials required to treat these infections are more expensive, can often only be administered intravenously, and tend to be associated with side effects requiring regular monitoring
        - Drug-drug interactions associated with newer antibiotics may complicate management of immunosuppression
        - If adherence to infection prevention activities is poor there is a risk of cross-transmission to other patients
    - Patients acquiring HAI are at greater risk of having an infection caused by an antibiotic resistant bacteria further complicating their hospital stay

3. What are we currently doing to manage the risk?

- We have infection prevention and control policies and procedures in place to identify patients at risk of colonisation with antibiotic resistant bacteria.
    - Active screening
    - Management with transmission-based precautions
    - Hand hygiene programme
    - Environmental cleaning with vapourised hydroden peroxide
- Regular monitoring of AMR trends at Auckland DHB
- Antimicrobial stewardship
    - Using antimicrobials wisely
    - Guidance on the treatment of serious infections

[11] Baker MG, Barnard LT, Kvalsvig A et al. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. Lancet 2012; 379: 1112-9

Figure 4. New Zealand Antimicrobial Resistance Timeline